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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/776,504	02/12/2004	Ralph M. Ellison	077319-0399	3667

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EXAMINER	
PAK, JOHN D	

ART UNIT	PAPER NUMBER
1616	

DATE MAILED: 06/02/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/776,504	ELLISON ET AL.	
	Examiner	Art Unit	
	JOHN PAK	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *17,18 and 23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16,19-22 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/04, 10/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Claims 1-24 are pending in this application.

Applicant is requested to update the continuity data in the specification by including the patented status of the parent application.

Applicant's election with traverse of the invention of Group I (claims 14-16) in the response filed on 3/15/2006 is acknowledged. Applicant argues that a separate and divergent search would not be required because a generalized search of the subject matter of any one of the invention groups would necessarily lead to disclosures encompassed by the other invention groups. Applicant further states that similar classification of the inventions is evidence of "recognition in the art of a single subject of inventive effort." Accordingly, applicant concludes that search and examination of the entire application would not impose a serious burden on the Examiner. The Examiner cannot agree.

First, applicant's statements are inconsistent with applicant's own prior actions. Applicant has claimed the following in four separately filed patent applications:

Application No.	**Claimed subject matter**
10/640,399	Treatment of multiple myeloma with arsenic
10/649,944	Treatment of lymphoma with arsenic
10/649,776	Treatment of melanoma with arsenic
10/640,403	Treatment of myeloid dysplastic syndrome with arsenic

If indeed there were such "recognition in the art of a single subject of inventive effort" for treatment of all cancer types with arsenic, applicant's separate filing of four different applications directed to four different types of cancers or pre-cancerous conditions is direct contrary evidence against applicant's arguments here.

Second, the U.S. Patent Classification system is not always indicative of the divergent searches and complex technology-specific considerations that would be required. This is particularly the case in complex technologies where the classification system has not kept up with the developments in the art. For example, applicant argued during the prosecution of 10/649,776 that even a prior art reference that explicitly discloses "body surface tumors" and "skin cancer" is distinguishable over a claim directed to melanoma because there are many different types of skin cancers, such as basal cell carcinoma, squamous cell carcinoma, cutaneous T-cell lymphomas, Kaposi's sarcoma (reply filed on 3/7/2006). Applicant argued that different approaches are taken towards treating different types of skin cancer and the prior art disclosure of "body surface tumors" and "skin cancer" fails to provide reasonable expectation of success for treating melanoma. Clearly, applicant's arguments there are squarely in contradiction of applicant's argument in this application. The same inventors clearly recognized a separate inventive effort even among different types of skin cancers. For applicant to argue that there is not a separate inventive effort here is difficult to accept

or understand, when the types of cancers covered here are far more divergent than mere skin cancer types.

Applicant also argues that the search and examination of the four invention groups would not impose a serious burden on the Examiner. The Examiner cannot agree. As shown above, the examination of this application may turn on the preciseness of prior art teachings and technology-specific issues, and the burden represented by having to separately search AND separately consider the various different types of cancers to be treated vis-a-vis the prior art would place an undue burden on the Examiner. Undue burden is a relative and balanced concept since if the Examiner were given several weeks of time to search and examine this application, the burden would decrease. Applicant should keep in mind that this Examiner is given less than 14 hours to complete this case, from start to finish (allowance, abandonment or Examiner's Answer). Undue burden is also in plain view just from applicant's several information disclosure statements: 8 pages worth of prior art listing were submitted. With so much relevant prior art and so many different types of cancers to consider, the specifics of this application support the Examiner's previous determination of undue burden.

Applicant's traversal of the outstanding restriction requirement is therefore found unpersuasive and the restriction requirement of record is thereby made FINAL.

Examination of this application shall be limited to the elected subject matter. Claims 1-16, 19-22 and 24 will presently be examined *to the extent* that they read on the elected subject matter. Claims 17-18 and 23 are withdrawn from further consideration as being directed to non-elected subject matter.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 11 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 11 recites all-trans retinoic acid (ATRA) as a "further therapeutic agent" when it is already being administered as part of the required regimen in claim 1. This renders the claim confusing and indefinite.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-7, 13-15, 20-21, 24 are rejected under 35 U.S.C. 102(a) as being anticipated by Shen et al.[1]

Shen et al. explicitly disclose intravenously administering 10 mg arsenic trioxide in glucose and saline to patients who have APL, acute promyelocytic leukemia (which is

a type of acute myelogenous leukemia, AML). See the entire article, in particular page 3354, right column, last paragraph. All patients were previously treated with ATRA (page 3358, right column, lines 8-11). Two patients were treated with ATRA during the remission induction period (page 3358, right column, lines 21-31; see also page 3356, left column, lines 8-9).

Shen et al. clearly anticipated the instant claims. Same exact drugs were administered to the same subjects to treat the same cancer. Refractory feature of claim 24 is met because Shen's patients who received both arsenic trioxide and ATRA did not respond to ATRA alone (page 3358, right column, lines 23-25).

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-16, 19-22 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shen et al. in view of Chen et al., Kwong et al., and Medline abstract 91278513.

Shen et al. disclose intravenously administering 10 mg arsenic trioxide in glucose and saline to patients who have APL, acute promyelocytic leukemia (which is a type of

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[1] Shen et al., Blood, Vol. 89(9), May 1, 1997, pages 3354-3360, cited by applicant in the IDS of 5/19/04.

acute myelogenous leukemia, AML). See the entire article, in particular page 3354, right column, last paragraph. All patients were previously treated with all-trans retinoic acid, ATRA (page 3358, right column, lines 8-11). Two patients were treated with ATRA during the remission induction period (page 3358, right column, lines 21-31; see also page 3356, left column, lines 8-9). Shen's patients who received both arsenic trioxide and ATRA did not respond to ATRA alone (page 3358, right column, lines 23-25). Other patients received danorubicin + cytosine arabinoside, harringtonine or hydroxyurea in addition to arsenic trioxide (Table 2 on page 3355).

Chen et al.[2] disclose arsenic trioxide to be effective and relatively safe in the treatment of APL (abstract, pages 3351-52). Arsenic trioxide as a dose-dependent dual effect on APL cells, wherein apoptosis occurs at higher concentrations and differentiation occurs at lower concentrations (page 3351, left column, last full paragraph). Partial differentiation of APL cells followed by cell death is also disclosed (id.). Lack of cross-resistance is disclosed between arsenic trioxide and all-trans retinoid acid (page 3345, left column, second paragraph).

Kwong et al.[3] disclose the use of arsenic trioxide for treating chronic myeloid leukemia (CML) and acute myeloid leukemia (AML). See page 3487. 10 mg/day of arsenic trioxide via IV resulted in complete morphologie remission in acute

[2] Chen et al., Blood, Vol. 89(9), pages 3345-53, cited by applicant in the IDS of 5/19/04.
[3] Kwong et al., Blood, Vol. 89, pages 3487-88 (May 1997), cited by applicant in the IDS of 5/19/04.

promyelocytic leukemia (APL) patients (left column of page 3487, first paragraph). Arsenic trioxide is disclosed as "effective for leukemias.of different morphologie types" and such activity is disclosed to be related to intrinsic toxicity of arsenic to marrow cells (page 3487, right column). Arsenic trioxide is also disclosed to induce apoptosis and differentiation of APL cells (page 3487, right column, last sentence).

Medline abstract 91278513 discloses efficacy of ATRA in the treatment of CML.

It is the Examiner's position that Shen et al. anticipate claims 1-7, 13-15, 20-21, 24, as stated above in the previous ground of rejection, so there is no patentable difference as to those claims. Under obviousness analysis, those same claims would have been obvious because Shen et al. provide exactly the same disclosure, as discussed above.

The difference between the claimed invention and the cited references is that the references do not explicitly disclose several of the dependent claim features.

The cited references do not explicitly disclose a further combination of at least one more therapeutic agent as set forth in applicant's claims 9-11. However, such combination therapies would have been fairly suggested from the conventional practice in the cancer treatment field to combine the actions and benefits of several therapies to attack the cancer cells from a variety of mechanisms. A substance such as cisplatin is a well known anticancer agent and its use in combination with arsenic trioxide and

ATRA would have been obvious from the motivation to control the cancer cells via various approaches.

Applicant's claim 12 recites dosing based on body weight. Such dose adjustment would have been obvious from the motivation to tailor the amount of the arsenic trioxide to obtain the maximum therapeutic benefit while keeping side effects to tolerable levels. Smaller individuals who weigh less are less likely to tolerate higher amounts, so it would have been obvious to vary the dose according to body weight.

Applicant's claim 16 recites treating CML. However, the cited references clearly establish that both arsenic trioxide and ATRA are known to have efficacy against both AML and CML. Hence, the ordinary skilled artisan would have been motivated to treat CML with a combined therapy of arsenic trioxide and ATRA.

Motivation to treat metastasized cancer would have been found from the efficacy of these combination treatments against various anti-cancer mechanisms.

Timing of ATRA treatment would have been within the skill of the ordinary skilled artisan, who would have been motivated to use the treatment before, after or concurrently with arsenic trioxide depending on patient condition and the severity of leukemia.

Therefore, the claimed invention, as a whole, would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, because

every element of the invention and the claimed invention as a whole have been fairly disclosed or suggested by the teachings of the cited references.

Claims 1-16, 19-22 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shen et al. in view of Chen et al., Kwong et al., Medline abstract 91278513 and Witte et al. (US 4,599,305).

Teachings of all references except for Witte et al. were discussed above, and the discussion there is incorporated herein by reference.

Witte et al. establish that various treatments are known for leukemia treatment, wherein acute leukemia "requires immediate treatment utilizing the full range of therapeutic measures available," such as radiation therapy and chemotherapy (column 1, lines 32-45). Radiation is used to treat both chronic lymphoid leukemia and acute leukemias (id.).

The Examiner incorporates herein by reference the full rationale set forth in the immediately preceding ground of rejection. Witte et al. add to the understanding of the level of the skill of the ordinary skilled person in this art by further making clear that combination of multiple treatment agents for leukemia would have been fairly suggested from the conventional practice in the leukemia treatment field to combine the actions and benefits of several therapies to attack the cancer cells from a variety of mechanisms.

Therefore, the claimed invention, as a whole, would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, because every element of the invention and the claimed invention as a whole have been fairly disclosed or suggested by the teachings of the cited references.

Applicant is further advised that numerous references cited on PTO-1449 were crossed out because they were listed more than once, they were relisted as published patent documents, or they were foreign language documents that did not meet the IDS requirements for proper consideration. A search report cannot be used to indicate relevance when it is not a *counterpart* application.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to JOHN PAK whose telephone number is **(571)272-0620.** The Examiner can normally be reached on Monday to Friday from 8 AM to 4:30 PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's SPE, Johann Richter, can be reached on **(571)272-0646**.

The fax phone number for the organization where this application or proceeding is assigned is **(571)273-8300**. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-1600. Information regarding the status of an application may be

obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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